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CONCISE COMMUNICATION

Inappropriate Use of Antifungal Medications in a Tertiary Care Center in Thailand: A Prospective Study

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The incidence and factors associated with inappropriate use of antifungal medications were studied in a Thai tertiary care center. The incidence of inappropriate antifungal use was 74% (in 42 of 57 patients). Isolation of *Candida* species from urine ($P = .004$) was a risk factor, whereas receipt of an infectious diseases consultation ($P = .004$) was protective.

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It is well recognized that inappropriate antifungal use contributes to the global increase in antifungal resistance and may lead to a variety of adverse outcomes, including unnecessary exposure to medications, persistent infections, and increased costs.[1] This issue has been particularly concerning in developing countries, where antifungal management programs rarely exist. Despite these concerns, the data are limited on the incidence and prevalence of inappropriate antifungal use and the risk factors associated with it. We conducted a prospective study from December 1, 2006, to June 30, 2007, to assess the incidence of and factors associated with inappropriate use of antifungal medications at a hospital in Thailand.

METHODS

This study was conducted at Thammasart University Hospital, a 500-bed tertiary care university hospital in central Thailand. Routine antifungal susceptibility testing is performed according to Clinical and Laboratory Standards Institute (CLSI) criteria.[2] Both adult and pediatric infectious diseases consultation services are readily available. There were no existing policies for antifungal drug use at our hospital during the study period. All hospitalized inpatients at least 15 years old who were prescribed antifungal therapy were included. Inpatients receiving oral or intravenous antifungal medications were monitored by the study team until discharge. Each patient who received antifungal therapy was visited 3 times: when the patient first had the antifungal administered; when microbiologic laboratory results (ie, culture results) were available (72 hours to 1 week after sampling, depending on fungal pathogen); and at discharge when the final diagnosis was available. Data were collected regarding each patient's demographic characteristics, comorbidities, and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, and the antifungal agent prescribed, indication for antifungal prescription, request for infectious diseases consultation, appropriateness of antifungal use, and reasons for any inappropriate antifungal use. Through a review of the medical records, antifungal therapy was classified as empirical treatment for a suspected infection, prophylaxis for fungal opportunistic infection, or treatment for a documented fungal infection. All data were collected by one investigator (A.S.) and recorded into a data collection tool. The prescribing physicians were unaware that the study was being performed at the time of medical chart review. The hospital's institutional review board approved the study.

The criteria used to define the appropriateness of antifungal prescription were adopted from the current edition of *Principles and Practices of Infectious Diseases*.[3] Specific use categories were modeled after those of Kunin et al.[4] and were modified to fit local practices by an expert panel consisting of 2 infectious diseases physicians who were not directly involved in the clinical care of the study patients. Significant candiduria was defined as a *Candida* concentration of at least 10^5 cfu/mL in a urine sample. Diagnosis of significant candiduria also required evidence of urinary tract pyuria (defined as a white blood cell count of at least 10 cells/mm^3, or at least 3 white blood cells per high power field of unspun urine), and recovery of identical *Candida* isolates from multiple urine samples and/or from samples of blood and urine.[5,6] Measurements were performed by 2 investigators and any discordance in the assessment of appropriateness was mediated by a third infectious diseases specialist.

Categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate, and continuous variables were compared using the Mann-Whitney *U* test. To evaluate the risk factors associated with inappropriate antifungal use, variables that were present for more than 10% of patients and that had a *P* value of greater than .20 on univariate analysis or that had *a priori* clinical significance were entered into backward stepwise logistic regression models. Significant variables that were potential covariates were grouped, and only 1 variable from each group was chosen for entry into the model. The final model was chosen on the basis of biological plausibility and by selecting the logistic regression model with the lowest -2 log likelihood function. All tests were 2-tailed, and *P* values less than .05 were considered to be statistically significant.

RESULTS

During the study period, antifungal medications were prescribed for 57 patients. The most common sites from which fungus was isolated included the urine (22 [39%] of 57) and bloodstream (17 [30%] of 57). Of the 57 patients, 47 (82%) received antifungal medications for documented infections,

TABLE 1. Demographic and Clinical Characteristics of Patients Receiving Antifungal Prescriptions at Thammasart University Hospital

Characteristic	Patients with appropriate antifungal prescription (n = 15)	Patients with inappropriate antifungal prescription (n = 42)	P[a]
Age, years, median (range)	45 (15-75)	46 (22-79)	.65
Female sex	10 (67)	24 (57)	.52
APACHE II score, median (range)	10 (0-20)	9 (3-33)	.71
Diabetes mellitus	2 (13)	14 (33)	.15
Congestive heart failure	1 (7)	2 (5)	.77
HIV infection	5 (33)	8 (19)	.26
Chronic lung disease	1 (7)	6 (14)	.44
Immunocompromised state[b]	5 (33)	15 (36)	.86
Fungus isolated			.22
Candida albicans	5 (33)	17 (41)	
Non-*albicans* species of *Candida*	4 (27)	20 (48)	
Other[c]	6 (40)	5 (12)	
Site of isolation			<.001
Urinary tract	1 (7)	21 (50)	
Bloodstream	8 (53)	9 (21)	
Other[d]	6 (40)	12 (29)	
Admission ward			.68
Medicine	11 (73)	33 (79)	
Surgery	3 (20)	8 (19)	
Other[e]	1 (7)	1 (2)	
Prescriber of antifungal(s)			.65
Attending physician	1 (7)	3 (7)	
Resident physician	3 (20)	6 (14)	
Intern	11 (73)	33 (79)	
Infectious diseases consultation received	14 (100)	3 (7)	<.001

NOTE. Data are no. (%) of patients, unless otherwise noted. APACHE II, Acute Physiology and Chronic Health Evaluation II.

[a] Determined by use of Fisher exact test, for proportion variables, and the Mann-Whitney U test, for continuous variables.

[b] Includes patients who received chemotherapy, immunosuppressive medications, or long-term steroid therapy (>2 weeks) and neutropenic status.

[c] *Cryptococcus neoformans* and *Aspergillus* species.

[d] Respiratory tract, cerebrospinal fluid, ocular infection, and skin or wound infection; also includes antifungal medication as prophylaxis or empirical therapy.

[e] Pediatrics, orthopedics, rhinootolaryngology, and obstetrics and gynecology wards.

6 (11%) received antifungals as prophylaxis, and 4 (7%) received antifungals as empiric therapy. The overall incidence of inappropriate antifungal use was 74% (in 42 of 57 patients). Inappropriate antifungal therapy was identified in 29 (51%) of the 57 patients at the time the antifungal was first administered, in 31 (54%) at the time when microbiologic laboratory results became available, and in 38 (67%) at discharge. Notably, 21 (72%) of 29 patients who initially received an inappropriate antifungal continued to receive an inappropriate antifungal at discharge. The most common reasons that antifungal use was inappropriate were as follows: unnecessary administration of antifungal agents (in 13 [31%] of 42 patients), lack of renal dose adjustment (in 12 [29%] of 42 patients), and inappropriate dose and duration (overdose or inadequate dose and/or inadequate or unnecessarily prolonged duration) (in 3 [7%] of 42 patients). There was 100% agreement in the assessment of antifungal use by the 2 investigators. Seventeen (30%) of 57 patients received an infectious diseases consultation. The proportion of patients who received an infectious diseases consultation in the medical and in the surgical services did not differ significantly (14 [32%] of 44 vs 3 [27%] of 11; P = .77). Table 1 compares the characteristics of patients who received appropriate antifungal prescriptions with those of patients who received antifungals inappropriately, and Table 2 summarizes the incidence of and reasons for inappropriate antifungal prescriptions.

By multivariate analysis, a urine culture positive for *Candida* species (adjusted odds ratio [aOR], 7.1 [95% CI, 1.9-

TABLE 2. Incidence of and Reasons for Inappropriate Antifungal Prescriptions, Stratified by Site of Fungal Isolation

Variables	No. (%) of patients, by site(s) of isolation			
	Any site	Urine	Bloodstream	Other[a]
Inappropriate antifungal prescription received	42 (100)	21 (50)	9 (21)	12 (29)
Admission ward				
Medicine	33 (79)	16 (76)	5 (56)	12 (100)
Surgery	8 (19)	5 (24)	3 (33)	…
Other[b]	1 (2)	…	1 (11)	…
Antifungal medication				
Amphotericin B	13 (31)	2 (10)	5 (56)	6 (50)
Fluconazole	27 (64)	19 (90)	4 (44)	4 (33)
Other[c]	2 (5)	…	…	2 (17)
Reason for inappropriate prescription				
Unnecessary	13 (31)	8 (38)	0 (0)	4 (33)
Lack of renal dose adjustment	12 (29)	4 (19)	6 (67)	3 (25)
Inappropriate dose and duration	3 (7)	1 (5)	2 (22)	…
Other[d]	14 (33)	8 (38)	1 (11)	5 (42)

[a] Respiratory tract, cerebrospinal fluid, ocular infection, and skin or wound infection; also includes use of antifungal medication as prophylaxis or empirical therapy.
[b] Pediatrics, orthopedics, rhinootolaryngology, general practice, and obstetrics and gynecology wards.
[c] Itraconazole, voriconazole, or caspofungin.
[d] Treatment inconsistent with hospital guidelines, antifungal with too broad a spectrum, pathogen resistant to the antifungal, patient allergic to the antifungal, and antifungal unable to penetrate to infection site.

59.3]; $P = .004$) was associated with inappropriate antifungal use, whereas receipt of an infectious diseases consultation was protective against inappropriate use (aOR, 0.71 [95% CI, 0.32-0.94]; $P = .004$). Although the association was not statistically significant, patients with an APACHE II score greater than 15 were more likely to receive inappropriate antifungal therapy than were patients with a lower score (aOR, 3.6 [95% CI, 0.9-15.6]; $P = .07$). Patients who had urine culture positive for *Candida* species were more likely to have a central venous line or a urinary catheter than were those without such a culture result (OR, 4.5 [95% CI, 1.2-52.4]; $P = .01$), and patients who had an APACHE II score of greater than 15 were more likely to develop renal failure during the hospitalization than were those with a lower score (OR, 5.1 [95% CI, 1.05-46.2]; $P = .03$).

DISCUSSION

Felix and colleagues[7] first reported an audit of antifungal use in a tertiary care university hospital in the United Kingdom. The incidence of inappropriate use of antifungal medications was 67%. The most common reasons that antifungal use was inappropriate were inappropriate dose and duration (41%) and inappropriate indication (27%). In Thailand, although many studies regarding the incidence and prevalence of and risk factors for inappropriate antibiotic use have been reported,[8] these studies have not examined the appropriateness of antifungal therapy. To our knowledge, we are the first to describe the high incidence of inappropriate antifungal use in Thailand and emphasize the need to have an antifungal management program.

Although the small sample size may limit our capacity to detect other potential risk factors, our data reveal significant associations between inappropriate antifungal use and the isolation of fungus from the urine and a higher APACHE II score. These associations are not surprising, because most patients with candiduria had central line or urine catheters placed, which led to an increase in the rate of colonization and unnecessary treatment. Patients with a higher APACHE-II score had been exposed to antibiotics, which led to an increase in the rate of colonization and also a higher incidence of renal failure requiring renal dose adjustment. Importantly, patients who initially received inappropriate antifungal therapy tended to receive inappropriate antifungal therapy throughout their hospitalization. As has been consistently shown in studies from developed countries,[9,10] this study also suggests the benefit of an infectious diseases consultation in guiding appropriate antifungal use in developing countries.

Given the findings of our study, attempts to rectify the inappropriate use of antifungal medications should be focused on educational interventions. The interventions should include dose adjustments in patients with renal failure, improvement in appropriate clinical recognition of significant candiduria, and establishment of antifungal management programs that incorporate infectious diseases consultations.

Further studies to evaluate factors associated with the inappropriate use of antifungal medications and interventions to reduce inappropriate antifungal use in developing countries are needed.

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REFERENCES

1. Loeffler J, Stevens DA. Antifungal drug resistance. *Clin Infect Dis* 2003; 36(suppl1):S31-41.
2. NCCLS. Methods for antifungal disk diffusion susceptibility testing of yeasts: Approved guideline. NCCLS document. Wayne, PA: NCCLS, 2004:M44-A.
3. Mandel GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 6th ed. New York, NY: Churchill Livingstone; 2005.
4. Kunin CM, Tupasi T, Craig WA. Use of antibiotics: a brief exposition of the problem and some tentative solutions. *Ann Intern Med* 1973; 79: 555-560.
5. Warren JW, Abrutyn E, Hebel JR. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis. *Clin Infect Dis* 1999; 29:745-758.
6. Lundstrom T, Sobel J. Nosocomial candiduria: a review. *Clin Infect Dis* 2001; 32:1602-1607.
7. Gutierrez F, Patrick GW, Cohen J. Antimicrobial practice: an audit of the use of antifungal agents. *J Antimicrob Chemother* 1996; 37:175-185.
8. Apisarnthanarak A, Danchaivijitr S, Bailey TC, Fraser VJ. Inappropriate antibiotic use in a tertiary care center in Thailand: an incidence study and review of experience in Thailand. *Infect Control Hosp Epidemiol* 2006; 27:416-420.
9. Classen DC, Burk JP, Wenzel RP. Infectious diseases consultation: impact on outcomes for hospitalized patients and results of a preliminary study. *Clin Infect Dis* 1997; 24:468-470.
10. Petrak RM, Sexton DJ, Butera ML, et al. The value of an infectious diseases specialist. *Clin Infect Dis* 2003; 36:1013-1017.